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EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 10/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/758,329	BONDAREV ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *3, 5, 18, 20, 30-35, and 41-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6-17,19,21-25,28,29 and 36-40* is/are rejected.

7)☒ Claim(s) *2, 17, 24, 26-28, and 37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group II, Claims 1, 2, 4, 6–17, 19, 21–29, and 36–40, in the reply filed on July 28, 2005, is acknowledged.

The traversal is on the ground(s) that the subject matter of pending claims 1–58 is sufficiently related so that no search burden exists. Further, Applicants suggest that the Examiner has made unsupported allegations that the different inventions have "different effects."

Applicants' arguments have been fully considered but are not found persuasive. The Examiner adamantly disagrees with Applicants' assertions and points to the 14-page Restriction Requirement, mailed on June 28, 2005, as ample support for reasons why the different inventions are considered to be independent or distinct. Inventions I–V, for example, which applicants argue should be examined together because they belong to the same class, comprise the use of structurally and functionally distinct molecules: antisense nucleic acids, nucleoside analogs, peptides, antisense-expressing constructs, and ribozyme-containing antisense nucleic acids. These act on different biochemicals, have different potencies and turnover rates, and, therefore, have the potential to elicit different types of effects in cells, tissues, and individuals.

Additionally, classes 514 and 435 each contain multiple inventions, which require further sorting by keyword and keyword combinations to identify pertinent art. A single search of LINE-1, for example, might reveal art related to the use of an inhibitor of LINE-1, but it would be insufficient in the instant case to identify all art having to do with particular antisense molecules, nucleoside analogs, peptides, or ribozymes.

Moreover, Applicants are reminded that claims 1 and 16 link inventions I–III. If these claims are held allowable the inventions will be rejoined, as explained in the previous Restriction Requirement.

For the reasons given above, and for the reasons stated in the previous restriction requirement, the requirement is still deemed proper and is therefore made FINAL.

Status of the Application

Claims 1–58 are pending. Claims 3, 5, 18, 20, 30-35, and 41-58 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant timely traversed the restriction (election) requirement in the reply filed on July 28, 2005.

Claims 1, 2, 4, 6-17, 19, 21-29, and 36-40 are examined herein, below.

Claim Objections

Claims 2, 17, 24, 26–28, and 37 are objected to because the claims recite limitations to non-elected inventions such as an antisense sequence or an antisense compound, a construct capable of expressing human L1RT antisense sequence, an inorganic compound, and peptide. Claims 26–28 recite limitations of non-elected inventions. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 6, 7, 19, 21–23, and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 19 recite the limitations "the nucleic acid" and "the DNA." There are insufficient antecedent bases for these limitations in the claims.

Claims 6, 7, 21, and 22 recite the limitation "the organic compound." There is insufficient antecedent basis for this limitation in the claims.

Claim 23 recites the limitation "the cancer." There is insufficient antecedent basis for this limitation in the claim.

Claim 28 is rejected under 35 U.S.C. 112, second paragraph, because the language of the claim is such that a person of ordinary skill in the art could not interpret the metes and bounds of the claim so as to understand how to avoid infringement (MPEP 2173.02). It cannot be presently determined what SEQ ID NO: Applicants are claiming since none has been recited. The claim appears to be incomplete. Correction is required.

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 6, 9, 10, 12-17, 19, 21, 23-25, 36, 37, 39, and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

The claims are drawn to methods for treating and preventing cancer in a human; to methods for interfering with the lengthening of telomeres in telomerase negative tumor cells; to methods for inhibiting the growth of telomerase negative cells; and to methods for inhibiting L1RT activity in a system competent to perform L1RT transcription. Independent Claims 1 and 16 comprise the step of administering to the individual or cells a therapeutically effective amount of an inhibitor of LINE-1 reverse transcriptase. Independent Claims 10, 24, 37, and 39 comprise

the step of simply contacting cells with, or of administering to the person a therapeutically effective amount of a nucleoside analog. Thus, the claims are broad, encompassing a genus of different methods using a wide variety of chemically and functionally distinct agents. For example, in their broadest embodiments, claims 1 and 16 encompass methods for treating cancer and inhibiting LINE-1 RT using any inhibitor of L-1 RT, including, but not limited to, nucleoside analogs, peptides, antibodies, nucleic acids, small molecule organic compounds, and inorganic compounds. Claims 10, 24, 37, and 39 are narrower than 1 and 16, but broad nevertheless, in that they encompass methods of treatment, inhibition, interference, and prevention using any nucleoside analog. Claims 10 and 39 limit the types of preventable cancers to those due to alternative lengthening of telomeres induced by L-1 RT.

Adequate written description does not exist in the instant application for all these methods. That is, the specification does not adequately allow persons of ordinary skill in the art to recognize that applicant(s) were in possession of the entire genus of methods as now claimed in the instant claims.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed (pg. 1117). Because the level of skill and knowledge in the art increases over time, it is essential to determine possession as of the effective filing date.

In the instant case, the specification does not clearly allow persons of ordinary skill in the art to recognize that Applicants invented what is now claimed. The application does not enable the skilled artisan to clearly envision the detailed chemical structure of the encompassed genus of

inhibitors and antagonists, including every conceivable nucleoside analog, polypeptide, antibody, nucleic acid, or inorganic compound that inhibit LINE-1 reverse transcriptase. Therefore, the skilled artisan could not clearly envision methods for using every conceivable inhibitor to treat or prevent any cancer in a human suffering from cancer.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

While the specification adequately describes 3 different nucleoside analogs, AZT, ddI, and d4T, and as many as six different antisense oligonucleotides by fully setting forth their structures and functions, and by describing the materials and methods needed to make and use such agents, adequate written description does not exist for the virtually unlimited number of other inhibitors and antagonists in the claimed genus. Thus, applicants have not shown possession of the claimed methods using every conceivable nucleoside analog, or any polypeptide or nucleic acid, to treat and/or prevent any type of cancer, as now claimed in claim 1, for example. Claims to the genus would be adequately described if the activity of each possible inhibitor in the claimed genus were known in the art or described in the instant application, or if it were known in the art or described in the instant application that each inhibitor in a given family of inhibitors, such as nucleoside analogs, within the claimed genus, possessed the same activity as that described in the instant application. However, there is no evidence to indicate that every nucleoside analog will be effective for the treatment or prevention of cancer or for interfering with the lengthening of telomeres in any telomerase-negative cell *in*

vitro and *in vivo*. No structure/function relationship has been disclosed by the Applicants such that one of skill in the art could immediately envision all other nucleoside analogs possessing the same anti-cancer properties as AZT, ddI, or d4T.

MPEP §2163 states, in part: "[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)."

In the instant case, the prior art indicates a degree of unpredictability in the art as it relates to the use of nucleoside analogs to suppress telomere lengthening and cell growth in cultured cells. Different nucleoside analogs can have different specific effects. For example, Strahl et al. report that ddG causes progressive telomere shortening but not observable effects on cell population doubling rates (*Molecular and Cell Biology* (1996) 16:53-65). AZT caused progressive telomere shortening in some but not all T- and B-cell cultures (Strahl et al.). Prolonged passaging in ddI did not cause reproducible telomere shortening or decreased cell growth rates or viabilities (Strahl et al.) In another case, AZT had no effect on telomere length in Skov-3 and Saos-2 cells (a telomerase-negative cell line), but resulted in significant telomere erosion in FaDu cells (Gan et al., 2002, *FEBS Lett.* 527:10–14).

Thus, the prior art indicates a fair degree of variability in the genus of nucleoside analogs. It must be concluded that similar if not greater levels of unpredictability exist in the art as it

relates to the use of such agents to treat or prevent cancer in humans. Because Applicants' disclosure does not reasonably lead the skilled artisan to any and all species of nucleoside analogs having the intended function, as now claimed, the skilled artisan would be required to conduct trial and error experimentation to find those having the desired function. However, a definition by function alone is not sufficient to meet the written description requirements.

Accordingly, only methods comprising the use of AZT, ddI, and d4T meet the written description requirement.

Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

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A further basis for lack of written description with respect to Claims 10–15, 39, and 40 is set forth as follows.

The instant claims are drawn to methods for treating or preventing any cancer in a human, wherein the cancer is due to cells showing alternative lengthening of telomeres induced or mediated by L-1 (LINE-1) retrotransposon encoded reverse transcriptase (RT).

Applicants have not described the genus of methods encompassed by these claims because Applicants have not described cancers that are "due to" or "induced by" LINE-1 RT. Applicants have not described or even alluded to a method for determining whether a particular individual is suffering or is prone to suffering from a form of cancer that is due to or induced by LINE-1 RT.

It is unclear from present disclosure and the state of the art at the time of filing how the skilled artisan would be able to determine whether the nascence of particular cancer was due to or induced by LINE-1 RT.

Post-filing art recognizes that cancer is a multifactorial event, in which numerous alterations contribute to the emergence of the malignant cell (Bocchetta et al., 2004, *Oncogene* 23:6484-6491). Malignant tumor growth is a dynamic process in which it is difficult to identify a unique event that caused the process (Bocchetta et al.).

The question is how does one determine that a particular cancer was induced by LINE-1 RT? Therefore, which cancers are treatable by the methods claimed in 10–15, 39, and 40?

The specification teaches (page 2) that up to 30% of human tumors of different types do not express telomerase, and that the presence of alternative lengthening of telomeres was reported in up to 30%, and possibly 50% of human tumors of different types. It is taught that L1RT is key factor in cancers of telomerase negative cells (page 9). Applicants teach that some cell lines are telomerase positive and some are telomerase negative (page 30), and that L1RT cancers can be induced in animal models. They further explain how to assay for telomerase activity in existing tumors (page 19).

Although this information is clearly important for Applicants' invention, it does not enable one of skill in the art to clearly recognize which cancers are treatable by the claimed methods, i.e., which cancers are due to or induced by LINE-1 RT.

Accordingly, Claims 10–15, 39, and 40 are rejected for failing to provide written description of methods for treating any and all cancers that are due to alternative lengthening of telomeres induced or mediated by LINE-1 RT, because no such cancers have been identified

with reasonable clarity such that the skilled artisan would recognize that Applicants were in possession of the claimed methods.

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Claims 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The claims are drawn to a method for preventing cancer in a person in need thereof, wherein the cancer is due to cells showing alternative lengthening of telomeres induced or mediated by LINE-1 RT, comprising administering to the person a therapeutically effective

amount of a composition comprising one or more nucleoside analogs. More specifically, the method is drawn to the prevention of those cancers listed in claim 40.

Therefore the invention is in a class of invention that the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The instant claims are very broad. For instance, in their broadest embodiments, the claims encompass methods for prevention of any cancer using any nucleoside analog or combination of analog.

A thorough search of the prior art did not identify any explicit teachings stating that cancer of any form is preventable via administration of nucleoside analogs, as now claimed in claim 39. However, post-filing art indicates that the treatment of cancer is highly unpredictable. Cancer is recognized to be a multifactorial event, in which numerous alterations contribute to the emergence of the malignant cell (Bocchetta et al., 2004, *Oncogene* 23:6484-6491). Malignant tumor growth is a dynamic process in which it is difficult to identify a unique event that caused the process (Bocchetta et al.). Human tumors of any given histological type have great genetic diversity, as revealed by gene expression profiling, and in most types of cancer only a subset of patients will prove responsive to any given agent (Chabner et al., 2005, *Nature Reviews Cancer* 65-72).

In view of these teachings, use of the claimed invention to treat cancer, least of all to prevent cancer, is considered to be highly unpredictable.

A review of the instant application (specifically at pages 29–31) finds one working example directed to the use of nucleoside analogs to inhibit cell growth in cultured cell lines. However, it is unclear how these *in vitro* results can be extrapolated to the claimed method of prevention of cancer in a human being. No additional guidance is provided in the specification as to how to use nucleoside analogs to prevent cancer, other than general assertions such as, for example, nucleoside analogs can be used to block ALT cancer (page 9), and AZT may be used to inhibit L1RT activity, apparently responsible for ALT.

Considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to practice the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 6, 7, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Rideout et al. (US Patent 5,683,990), which is cited in the instant application at page 10 and is characterized by Applicants as a reference describing AZT formulations.

Rideout et al. teach a method of treating a human being infected with HTLV-III, comprising the administration of an effective amount of 3'-azido-3'-deoxythymidine (AZT) and another compound, whose formula is disclosed at column 11. Detailed descriptions of suitable effective dosages of AZT and methods for formulating AZT for administration are provided (columns 9-10). Importantly, Rideout et al. teach that AZT and pharmaceutically acceptable salts thereof are also useful in treating Kaposi's sarcoma (KS) in human beings, and that this is another feature of their invention (columns 8-9). They further teach that the suitable effective dose for this indication [the treatment of KS] is the same as that used in the treatment of human beings infected with HTLV-III. They clearly recognize, with an explicit statement to the fact, that HTLV III infected patients often develop cancers such as Kaposi's sarcoma and Epstein-Barr virus-related lymphomas (column 1). At column 3, it is taught that AZT may be administered orally, topically, or intramuscularly.

Accordingly, the instant claims are anticipated by Rideout et al.

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Claims 16, 17, 21, 22-24, 29, 36–38 are rejected under 35 U.S.C. 102(a) as being anticipated by Gan et al. (2002) *FEBS Lett.* 527:10–14.

Gan et al. teach a method for administering AZT to telomerase positive and telomerase negative cell lines, including a Saos-2 osteosarcoma cell line, in culture, in an amount effective

to interfere with L1RT activity. Claim 37 recites a method for interfering with L1RT activity in a system competent to perform L1RT transcription. Each of the disclosed cell lines is considered by the Examiner to be "competent to perform L1RT transcription" as recited in claim 37, given that the instant application does not define the meaning of the term "competent" and given that the ordinary dictionary meaning of the term is simply "properly or sufficiently qualified," "capable," or "adequate for the purpose." (citation attached) In addition, the instant application teaches (page 30) that Saos-2 osteosarcomas produce L1 specific RNA, confirming their competency.

Gan et al. teach that the telomerase-positive cell lines were treated with at least 5 different concentrations of AZT in the range of 0.01 and 100 micromolar (Fig. 2 and 4). The telomerase-negative cell line, Saos-2 cells, were treated with 0, 1 and 10 micromolar AZT (see Fig. 4A). This range is considered by the Examiner to be an amount "effective to interfere with L1RT activity," as required by claim 37, given that 1) the instant application provides no specific guidance as to what is meant by "effective amount"; 2) the specification teaches (page 9) that the concentration of nucleoside analogs required to inhibit L1RT activity can be several fold lower than that required to inhibit telomerase; and 3) the specification teaches that AZT will be useful in cancer at nanomolar levels (page 9 instant application). The application provides one working example (page 29-31) directed to the use of AZT *in vitro* to inhibit telomere lengthening in cultured cells; specifically Saos-2 cells. But this example provides no information concerning the concentrations of AZT used to produce the observed effects, shown in Fig. 2. Gan et al. clearly recognize that AZT inhibits both telomerase and reverse transcriptase (pages 10 and 11).

Although Gan et al. state that AZT treatment had no effect on telomere length in the one telomerase-negative cell line tested, Saos-2 cells, the Gan et al. teachings include all of the method step limitations recited in the instant claims, and would therefore be expected to inherently perform the intended function recited in the preambles of the instant claims.

It is noted that the teachings of Gan et al. appear to contradict the teachings of the instant application. Namely, Gan et al. teach that AZT has no effect on telomere length in Saos-2 cells, whereas Applicants teach that AZT does affect telomere length in Saos-2 cells (see Example 1, page 30).

Nevertheless, in view of the disclosure provided by Gan et al. showing the use of AZT in a telomerase-negative osteosarcoma cell line, the instant claims are anticipated by Gan et al.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10, 11, 13, 15-17, 21, 22, 24, 29, and 37-39 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Rideout et al. The basis for this rejection is found in MPEP §2112 (Requirements of Rejection Based on Inherency; Burden of Proof), cited below.

Claim 10 recites a method for treating cancer in a human, wherein the cancer is due to cells showing alternative lengthening of telomeres induced or mediated by LINE-1 reverse transcriptase. Claim 39 recites a method for the prevention of cancer wherein the cancer is due to cells showing alternative lengthening of telomeres induced by LINE-1 RT. Claims 16 and 24 recite methods for inhibiting the growth of, or interfering with telomere lengthening in, telomerase negative tumor cells.

The teachings of Rideout et al. are described in part above. With respect to the instant claims Rideout et al. further teach that AZT may be used in combination with interferon to treat human beings infected with HTLV-III, and that the suitable effective dose range of AZT is 5 to 250 mg per kg per day (column 9, top). In this regard, as explained above, Rideout et al. state that AZT is useful in the treatment of Kaposi's sarcoma (KS) in human beings and that the suitable effective dose for this indication is the same as that used in the treatment of humans infected with HTLV-III. Thus, these teachings meet the limitations of the instant claim 15.

Rideout et al. do not teach that KS is induced or mediated by LINE-1 RT, or that the neoplastic cells involved in KS are telomerase negative. On the other hand, a review of the instant application fails to find any disclosure clearly describing any human cancers that are induced by or mediated by LINE-1 RT, or any guidance as to which types of cancer cells do or do not express telomerase. Applicants teach only that (page 2) up to 30% of human tumors of

different types do not express telomerase, and that the presence of alternative lengthening of telomeres was reported in up to 30%, and possibly 50% of human tumors of different types. Applicants teach that some cell lines are telomerase positive and some are telomerase negative (page 30), and that L1RT cancers can be induced in animal models. They further explain how to assay for telomerase activity in existing tumors (page 19).

Based on Applicants' teachings and those of the prior art, it cannot be presently determined whether Kaposi's sarcoma is a telomerase negative or telomerase positive tumor. Furthermore, it cannot be presently determined if KS is induced or mediated by LINE-1 RT. According to Applicants' teachings, there is a 30-50% chance that KS does satisfy these criteria. Thus, there is prima facie evidence to suggest that Rideout et al. teach the use of AZT to treat humans afflicted with a cancer that is induced or mediated by LINE-1 RT, and that such cancers comprise cells that are telomerase negative. Stated another way, it cannot be determined unequivocally that Rideout et al. do not teach the use of AZT to treat telomerase-negative cell cancers.

Accordingly, in the absence of evidence to the contrary, the instant claims are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Rideout et al.

MPEP §2112 Requirements of Rejection Based on Inherency; Burden of Proof
A REJECTION UNDER 35 U.S.C. 102/103 CAN BE MADE WHEN THE PRIOR ART PRODUCT SEEMS TO BE IDENTICAL EXCEPT THAT THE PRIOR ART IS SILENT AS TO AN INHERENT CHARACTERISTIC

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also

apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims.

A REFERENCE TEACHING PRODUCT APPEARING TO BE SUBSTANTIALLY IDENTICAL IS MADE THE BASIS OF A REJECTION, AND THE EXAMINER PRESENTS EVIDENCE OR REASONING TENDING TO SHOW INHERENCY, THE BURDEN SHIFTS TO THE
APPLICANT TO SHOW AN UNOBVIOUS DIFFERENCE

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald,* 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rideout et al. (US Patent 5,683,990); and Mathias et al. (1991) *Science* 254:1808-1810.

The claims are drawn to a method for treating an individual suffering from cancer, comprising the administration of an inhibitor of LINE-1 reverse transcriptase. Claim 4 limits Claim 1 by stating that LINE-1 reverse transcriptase is encoded by an RNA transcribed from a DNA.

Rideout et al. are relied on for the reasons given above. Rideout et al. do not teach that LINE-1 reverse transcriptase is encoded by an RNA transcribed from a DNA.

Mathias et al. teach that L1 or LINE-1 elements are a large class of repeated mammalian DNA sequences that have structural similarities to retrotransposons. Further, it is taught that an ORF2 from a human L1 element encodes a reverse transcriptase activity. They state that evidence indicates that LINE-like elements encode RT and transpose about the genome through cytoplasmic RNA intermediates (page 1810). The art of molecular biology teaches that proteins are normally translated from RNA, which are normally transcribed from DNA.

Given the fact that L1 like elements are taught by Mathias et al. to be a source of RT activity, and that they are able transpose between DNA and RNA elements, it would be obvious

to one of skill in the art that L1 reverse transcriptase derives from L1 RNA transcribed from L1 DNA.

The skilled artisan reading Rideout et al. would be mindful of the fact that cells produce protein via translation of RNA, which is transcribed from DNA, and that any proteins affected by the AZT treatment of Rideout et al. would most likely be proteins that are produced in the cell according to the art-recognized manner.

Though the skilled artisan may not have recognized at the time the invention was made that AZT was inhibiting LINE-1 RT, encoded by RNA transcribed from DNA, the artisan would not have needed to, since the inhibitory effects of AZT were inherently present.

The skilled artisan would have been motivated to use AZT according to the method taught by Rideout et al. to treat an individual suffering from cancer, because Rideout et al. teach that AZT is useful in treating individuals having AIDS, many of whom suffer from Kaposi's sarcoma, and that AZT offers another potential benefit in that it is useful in treating Kaposi's sarcoma.

Similarly, the skilled artisan would have had a reasonable expectation of success given that Rideout et al. teach methods for administering AZT to humans, and given that Rideout et al. teach specific pharmaceutical formulations of AZT for use in treating humans.

As a result, the instantly claimed invention as a whole would have been *prima facie* obvious at the time the invention was made.

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Claims 1 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rideout et al. (US Patent 5,683,990); and Wagner et al. (1997) *Cancer Res.* 57:2341-5.

Claim 8 limits Claim 1, described above, by stating that the cancer is specifically breast carcinoma or any of the others listed in claim 8.

Rideout et al. are relied on for the reasons given above. Rideout et al. do not teach a method of treating an individual suffering from breast cancer, according to claim 8.

Wagner et al. teach a method for inhibiting the growth of a human breast cancer cell line, MCF-7, *in vitro* using AZT. Additionally, the authors show that AZT can be used to inhibit rat mammary carcinomas *in vivo*. Detailed dosage regimens and results are provided (pages 2341-4). Wagner et al. suggest (page 2341), based on their results, that AZT alone may have therapeutic potential as an anti-breast cancer chemotherapeutic agent.

It would have been obvious to one of skill in the art at the time the invention was made to combine the teachings of Rideout et al. with those of Wagner et al.

The skilled artisan would have been motivated to use the AZT treatment protocols taught by Rideout et al. to treat patients suffering from breast cancer, in a manner modeled after that taught by Wagner et al., since Wagner et al. show and explicitly state that AZT has therapeutic potential as an anti-breast cancer chemotherapeutic agent, and given that Rideout et al. teach that AZT may be used to treat retroviral infection and retroviral related diseases, including a cancer known as Kaposi's sarcoma.

The skilled artisan would have had a reasonable expectation of success given that Rideout et al. teach specific pharmaceutical formulations of AZT for use in humans, and teach methods for administering AZT to humans for purposes of treating HTLV infections and related

As a result, the instantly claimed invention as a whole would have been *prima facie* obvious at the time the invention was made.

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Claims 16 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gan et al. (2002) *FEBS Lett.* 527:10–14; and Mathias et al. (1991) *Science* 254:1808-1810.

The claims are drawn to a method interfering with the lengthening of telomeres in telomerase negative tumor cells, comprising the administration of an effective amount of an inhibitor of LINE-1 reverse transcriptase. Claim 19 limits Claim 16 by stating that the nucleic acid encoding the reverse transcriptase is a DNA, an RNA transcribed from the DNA, or a cDNA reverse transcribed from the RNA.

Gan et al. are relied on for the reasons given above. Gan et al. do not teach that LINE-1 reverse transcriptase is encoded by a DNA, for example.

Mathias et al. teach that L1 or LINE-1 elements are a large class of repeated mammalian DNA sequences that have structural similarities to retrotransposons. Further, it is taught that an ORF2 from a human L1 element encodes a reverse transcriptase activity. They state that evidence indicates that LINE-like elements encode RT and transpose about the genome through cytoplasmic RNA intermediates (page 1810). The art of molecular biology teaches that proteins are normally translated from RNA, which are normally transcribed from DNA.

Given the fact that L1 like elements are taught by Mathias et al. to be a source of RT activity, and that they are able transpose between DNA and RNA elements, it would be obvious

to one of skill in the art that L1 reverse transcriptase derives from L1 RNA transcribed from L1 DNA.

The skilled artisan reading Gan et al. would be mindful of the fact that cells produce protein via translation of RNA, which is transcribed from DNA, and that any proteins affected by the AZT treatment of Gan et al. would most likely be proteins that are produced in the cell according to the art-recognized manner.

Though the skilled artisan may not have recognized at the time the invention was made that AZT was inhibiting LINE-1 RT, encoded by a DNA, the artisan would not have needed to, since the inhibitory effects of AZT were inherently present.

The skilled artisan would have been motivated to use AZT according to the method taught by Gan et al. as a research tool to inhibit the lengthening of telomeres in telomerase-positive cell lines and , because Gan et al. teach that AZT can be used to inhibit telomere lengthening in some cell lines.

Similarly, the skilled artisan would have had a reasonable expectation of success given that Gan et al. teach methods for preparing, administering, and assaying AZT in cultured cell lines.

As a result, the instantly claimed invention as a whole would have been *prima facie* obvious at the time the invention was made.

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Claims 16 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gan et al. (2002) *FEBS Lett.* 527:10–14.

Claim 16 is described above. Claim 25 limits Claim 16 by stating that the cell is contacted with a nucleoside analog at a concentration of 0.2 micromolar.

Gan et al. are relied on for the reasons given above. Gan et al. do not teach a method of treating a telomerase-negative cell with 0.2 micromolar AZT.

However, Gan et al. do teach treating telomerase-negative cells with 0, 1, and 10 micromolar AZT, which constitutes a range encompassing the claimed concentration of 0.2 micromolar.

MPEP §2144.02, Section I, Overlap of Ranges states that:

"In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). "[A] prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a prima facie case of obviousness." In re Peterson, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). However, if the reference's disclosed range is so broad as to encompass a very large number of possible distinct compositions, this might present a situation analogous to the obviousness of a species when the prior art broadly discloses a genus. Id. See also In re Baird, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); MPEP § 2144.08."

Thus, a *prima facie* case of obviousness of the instantly claimed invention exists in view of the teachings of Gan et al.

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The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Hernandez and Perez (1997) *J. Eur. Acad. Dermatol. Vener.* 9:44–49, which is considered pertinent to claims 1, 2, 6, and 7.

Hernandez and Perez teach the administration of AZT, a nucleoside analog, in combination with alpha-2 interferon, in an amount effective to treat AIDS patients suffering from Kaposi's sarcoma (KS), a tumor of the vascular endothelium. (page 46-46; Table 2). Of the ten patients treated, one showed complete remission of KS and two showed partial remission. Regimens for treatment are provided in Table 2 and pages 46-47. The instant application teaches that AZT is an inhibitor of LINE-1 reverse transcriptase and that AZT contributes to telomere shortening (page 8, for example). Claim 7 in fact claims AZT as an inhibitor of LINE-1 reverse transcriptase. Thus, the method of treatment taught by Hernandez and Perez comprises the use of an inhibitor of LINE-1 reverse transcriptase, and the blockage of telomere lengthening, as recited in claim 1, would be an inherent feature of this treatment, since AZT would have performed this function then as applicants teach it is able to now.

Conclusion

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on Mon–Fri, 8:00 am–4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval system (PAIR). Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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September 28, 2005
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